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09/719,045	12/07/2000	Andrew Paul Chapman	CARP-0086	3379

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EXAMINER
SAUNDERS, DAVID A

ART UNIT	PAPER NUMBER
1644	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 719,045	Applicant(s) CHAPMAN et al
	Examiner SAUNDERS	Group Art Unit 1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 2/27/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-15 is/are pending in the application.

Of the above claim(s) 8-9 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-7, 10-15 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☑ Claim(s) 1-15 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Applicant's election of species A (bridging polymer is a straight or branched chain polyakylene) is acknowledged. Claims 1-7 and 10-15 read on the elected species.

Claims will also be examined for the genus.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The disclosure is objected to because of the following informalities: at page 6, line 2, it is deemed "bridie" should read as --bridge--.

Appropriate correction is required.

Claim 15 objected to under 37 CFR 1.75© as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim (i.e. claim 3). See MPEP § 608.01(n).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the

effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7, 10-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Rhind et al. (EP 0,384,624 or WO 90/09195, cited on form 1449).

Rhind et al. teach the coupling of two reduced Fab' SH fragments via a cross-linking agent which has a maleimidyl group at each end thereof. See Examples 1-3.

Applicant's claim 1, when read with the broadest definition of "polymer" contemplated by applicant (pages 6-7) is consistent with what is shown by Rhind et al. The cross-linking agents contemplated Rhind et al. (page 2, lines 5+) and exemplified by Rhind et al. (Example 1) encompass the C 4-20 alkylene chains contemplated by applicant (page 7). Page and line number references are given for the EP publication.

The alkylene chains of the cross-linking agents of Rhind et al. may be interrupted by the presence of hetero-atoms (page 2, lines 15+). The cross-linking agents have functional groups at each end which are derivatives of common homobifunctional cross-

linking agents (page 2, lines 21+). The cross-linking group of Rhind et al. bears an effector group/reporter group (page 2, lines 9 and 49+). The antibodies of Rhind et al. are directed to cell surface or soluble antigens (page 6, lines 13+).

From the above consideration, instant claims 1-7, 10-13 and 15 are anticipated. Note, the examiner finds nothing in instant claim 12 that rules out attachment of the effector/reporter group to the antibody via the cross-linker, as taught by Rhind et al.

Claims 1-3, 7, 10-13 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Huston et al. (5,534,254).

Huston et al. teach the production of sFv antibody fragments containing, in their C-termerials, a Cys residue with a free SH group. Such sFv constructs may be joined by a homobifunctional linker, such as bismaleimidohexane (col. 5, line 54) or MCA - Gly Ser 3 Gly 2 Ser 3 lys - MCA (col. 5, lines 60+ and col. 14, lines 41+). See also col. 23, under Part B. Applicant's definition of "polymer" is so broad that the hexane linker and the peptide linker are properly considered as linking polymers. Thus claims 1-2 and 15 are anticipated.

Claim 3 is included since a "heavy chain paired with a light chain" is reasonably considered to encompass their being "paired" in an sFv.

Claim 10 is included since the above MCA-peptide-MCA reagent contains "the residue of a homo.... bifunctional cross-linking reagent".

Claims 7 and 11 are included since the hexane linker fits within a scope of a C 4-20 polyakylene chain.

Regarding claim 12, Huston et al. teach coupling of effectors/reporters to their bispecific construct. See col. 10, lines 10+.

The antibodies of Huston et al. are directed to surface antigens of cancer cells and/or immune cells (col. 10, lines 7+; col. 15, lines 47+). Thus claim 13 is anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhind et al. or Huston et al., either in vivo of Akita et al. (5,968,511).

Rhind et al. Or Huston et al. have been cited supra against claims 1 and 13 for teaching the instant divalent antibody

fragments directed against cell surface antigens. Huston et al., in particular, teach antibodies directed to the cell surface antigen C-erb B-2 and related tumor antigens.

Akita et al. teach antibodies directed to the erb B2- erb B3 cell surface antigen complex. Such antibodies include antibody fragments and multispecific antibodies formed from fragments (col. 6, lines 31-37). The latter include bispecific antibodies having one arm directed against the erb B3 cell surface antigen and the other arm directed against a cytotoxic agent (col. 14, lines 40-58). The term "cytotoxic agent" would encompass TNF-alpha (taught at col. 9, lines 6-34 amend other agents taught at col. 14, lines 51-56).

From the teachings of either primary reference combined with Akita et al., it thus would have been obvious to provide a divalent, bispecific antibody, with one arm directed to a cell surface antigen, such as erb B2- erb B3 and the other to the cytotoxic agent TNF -alpha. This rejection is made on the basis that the term "divalent" in claim properly encompasses "bispecific". Note, nothing in claim 1 requires that the two arms of the divalent antibody recognize the same antigen.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huston et al. in view of Barbanti et al. (5,436,154).

Huston et al. have been cited supra against claims 1 and 13. They teach that their sFv constructs have superior in vivo pharmacokinetic properties (accelerated distribution and clearance rates) over F(ab)2 dimmers. See col. 9, lines 45-63.

Barbanti et al. teach antibodies to TNF-alpha. They teach (col. 5, lines 43-55) F(ab')2 fragments of such antibodies have an advantage of clearing from the circulation more rapidly than intact antibodies. Since Huston et al. teach that dimeric sFv constructs clear even mere rapidly than F(ab')2 fragments, it would have been obvious to provide a dimeric sFv construct specific for TNF-alpha to conduct the therapeutic treatments taught by Barbanti et al.

No claim encompassing a generic "polymer" in the interchain bridge is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D., whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday-Thursday from 8:00

a.m. to 5:30 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

D. Saunders:jmr

May 27, 2003

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644